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Survival After Photodynamic Therapy to Non-Pulmonary Metastatic Endobronchial Tumors

James S. McCaughan, Jr., MD, FACS, FACCP, FASLMS*

The Grant Laser Center and The Laser Medical Research Foundation, Columbus, Ohio 43215

Background: **For the past 15 years we have used photodynamic therapy (PDT) to treat endobronchial tumors. Unfortunately patients who have non-primary lung cancer metastatic to bronchi and who have failed other treatment regimens may not be offered endobronchial tumor management. Thirteen patients with endobronchial tumors metastatic from non-pulmonary primaries were treated with PDT. We: 1) evaluated the effects of PDT on the tumor, the quality of life, and the length of survival; and 2) compared their survival after PDT to that of 27 patients with stage IV primary endobronchial tumors treated with PDT after they failed all other treatment regimens.**

Materials and Methods: **Photodynamic therapy was performed using 630-nm light delivered through cylinder diffusing tip quartz fibers passed through the biopsy channel of a flexible bronchoscope after intravenous injection of the photosensitizer dihematoporphyrin ether. One to two days after PDT bronchoscopy was repeated and necrotic tissue was mechanically removed and, if necessary, that site or other new sites were treated. Two days after this another bronchoscopy was performed and the necrotic tissue was mechanically removed. Bronchoscopy was repeated one month after PDT and periodically thereafter as needed to re-treat symptomatic residual tumor. The percent obstruction of the bronchus due to tumor was estimated before and at the end of each bronchoscopy. Clinical effects were evaluated using Wilcoxon signed rank tests for scaled parameters of dyspnea, cough, hemoptysis, and Karnofsky Performance Status (KPS) before and one month after PDT. All patients were followed until their death.**

Results: **The mean percent obstruction due to metastatic non-pulmonary tumors at 38 different endobronchial treated sites decreased from 85% to 13% at discharge after PDT. The 72% mean decrease of obstruction was statistically significant using**

Abbreviations used: CF = centimeter length of diffuser fiber tip; DHE = dihematoporphyrin ether; KPS = Karnofsky Performance Status; J = Joules; LLL = left lower lobe bronchus; LMB = left main bronchus; LUL = left upper lobe bronchus; mW = milliwatts; NAP = not applicable; PDT = photodynamic therapy; RLL = right lower lobe bronchus; RMB = right main bronchus; RML = right middle lobe bronchus; RUL = right upper lobe bronchus

*Correspondence to: James S. McCaughan, Jr., MD, FACS, FACCP, FASLMS, The Grant Laser Center and The Laser Medical Research Foundation, 323 E. Town St., Columbus, Ohio 43215. E-mail: jmccaughan@iwaynet.net

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the Wilcoxon signed rank test ($P < .0001$). There was a statistically significant improvement in the level of dyspnea ($P = .012$), hemoptysis ($P = .028$), cough ($P = .027$), and KPS ($P = .020$). Kaplan-Meier survival curves and Mann-Whitney U rank tests showed the median survival of stage IV primary tumor patients (4 months) vs. metastatic tumor patients (14 months) was statistically significant ($P = .008$).
Conclusion: **PDT of endobronchial metastatic tumors effectively decreased the amount of endobronchial obstruction, and improved the quality of life. Lasers Surg. Med. 24:194–201, 1999.**

Key words: photodynamic therapy; dihematoporphyrin ether; metastatic endobronchial tumors; lung cancer survival

INTRODUCTION

Selective photodynamic therapy (PDT) to treat malignant tumors is based on three observations: 1) The photosensitizer disseminates to all cells after intravenous injection; 2) the photosensitizer is selectively retained in the tumor cells so there is a greater concentration of the photosensitizer in the tumor cells than in the adjacent normal tissue; 3) the photosensitizer absorbs light energy and produces singlet oxygen which destroys the tumor partly by causing thrombosis of tumor vessels. Since there is less photosensitizer in the adjacent tissue, it will react less.

Since 1982 we have used photodynamic therapy to treat endobronchial tumors in an ongoing study of its effectiveness.

MATERIALS AND METHODS

From 1983 to July 1995, 13 patients with endobronchial metastases from non-pulmonary tumors and 27 patients with stage IV primary endobronchial tumors were treated with PDT. This study was performed with the approval of the hospital Institutional Review Board. All patients were clinically staged at the time of their PDT using the TNM [1] system based on history, physical examination, bronchoscopy, and CT scans of the chest and abdomen.

Photodynamic therapy was performed using 630-nm light generated by an argon dye laser system (Spectra Physics, Mt. View, CA) as the activator and delivered through cylinder diffusing tip quartz fibers (CF) passed through the biopsy channel of a flexible bronchoscope. The cylinder diffusing tip was inserted into or placed alongside the tumor 2–168 h (mean = 31, median = 24, SD = 33) after injection of 2 mg/kg (median = 66 mg/m^2 of body surface) of the photosensitizer dihematoporphyrin ether (DHE, Quadra Logic Technologies, Vancouver, B.C.).

A power density of 400–700 mW/cm diffusing fiber (mean = 500, median = 500, SD = 43) delivered a light dosage of 230–500 J/cm of diffusing fiber (mean = 397, median = 400: SD = 63).

One to two days after PDT, bronchoscopy was repeated and necrotic tissue was mechanically removed and, if necessary, that site or other new sites were treated. Two days after this, another bronchoscopy was performed and the necrotic tissue was mechanically removed.

Bronchoscopy was repeated one month after PDT and periodically thereafter as needed to retreat symptomatic residual tumor. Twenty-five injections of DHE were made (mean = 2 injections/patient). The Karnofsky Performance Status (KPS) [2], amount of cough, hemoptysis, and dyspnea were recorded using ordinal scales at each visit and periodically during follow up. Scales for cough were 0 = none, 1 = mild, 2 = moderate, 3 = marked, 4 = severe. Scales for hemoptysis were 0 = none, 1 = streaks, 2 = drops, 3 = clots or more than drops, 4 = massive requiring transfusions. Scales for dyspnea were 0 = active asymptomatic with normal activity, 1 = symptomatic when ambulatory but not with normal activity, 2 = on minor exertion, 3 = without exertion, 4 = bedridden.

Biopsies and cytology washings were taken and the percent obstruction of the endobronchial sites was estimated at the beginning and end of each bronchoscopy. All patients were followed until their death.

Statistical Analysis

Statistical analyses using 95% confidence limits were performed using SuperANOVA, StatView, and Survival Tools (Abacus Concepts, Inc.,

TABLE 1. Demographics of Patients With Non-Pulmonary Tumors Metastatic to the Endobronchus

Patient number	Primary	Age/race/sex	Previous treatment	Date first endorx	Years after primary diagnosis	KPS[a] before	KPS 1 month	Hemoptysis before	Hemoptysis 1 month
1	Breast	58 WF	1978 Radical mastectomy, tamoxifen	11/10/83	5	80	90	2	0
2	Breast	82 WF	1977 Mastectomy, chemo, thoracentesis, and sclerosing	1/11/85	8	70	90	0	0
3	Breast	73 WF	1975 Mastectomy and X-ray; 1981 tamoxifen; 1983 X-ray ribs and right hilum	10/21/85	10	80	90	2	0
4	Colon	52 WF	1977 AP resection, 1979 liver resection, 1981 L lower lobectomy, chemo	3/17/83	6	20	90	0	0
5	Colon	65 WF	1985 Colon resection, chemo, X-ray to abdomen	4/14/86	1	70	80	1	0
6	Colon	61 WF	1988 Colon resection, 1990 left lung wedge resection	8/10/92	4	70	40	0	0
7	Colon	66 WM	1986 Colon resection, 1989 wedge resection RUL, 1992 wedge resection RLL	8/22/94	8	20	30	0	0
8	Gall bladder	91 BF	1988 cholecystectomy, chemo	8/26/93	5	40	60	3	0
9	Renal	53 WM	1988 Nephrectomy, chemo, X-ray	12/13/94	6	50	60	1	0
10	Urinary bladder	67 WM	1983 Bladder resection	8/11/95	12	30	50	2	1
11	Uterine leiomyosarcoma	57 WF	1978 Hysterectomy, 1985 thoracotomy and resection endobronchial tumor in RUL, chemo	8/29/86	8	70	90	1	0
12	Uterine leiomyosarcoma	84 WF	1978 Hysterectomy	6/7/89	11	60	90	0	0
13	Uterine leiomyosarcoma	59 WF	1984 Hysterectomy, chemo	6/4/91	7	40	90	0	0

	Dyspnea before	Dyspnea 1 month	Cough before	Cough 1 month	Survival after first PDT (months)	Cause death
1	0	0	2	0	7	DOD
2	2	0	2	0	21	DOD
3	2	0	2	1	17	DOD
4	4	1	2	1	15	DOD-liver METS
5	1	1	2	1	12	DOD
6	2	2	2	2	6	DOD
7	4	4	3	1	5	DOD-respiratory
8	4	2	2	0	4	DOD-refused further RX
9	3	2	2	2	6	DOD-respiratory
10	3	2	3	1	8	DOD-respiratory
11	2	0	2	2	26	DOD-liver METS
12	2	0	3	0	24	DOD-brain METS
13	3	1	2	2	14	DOD-brain METS

[a]KPS, Karnofsky Performance Status.

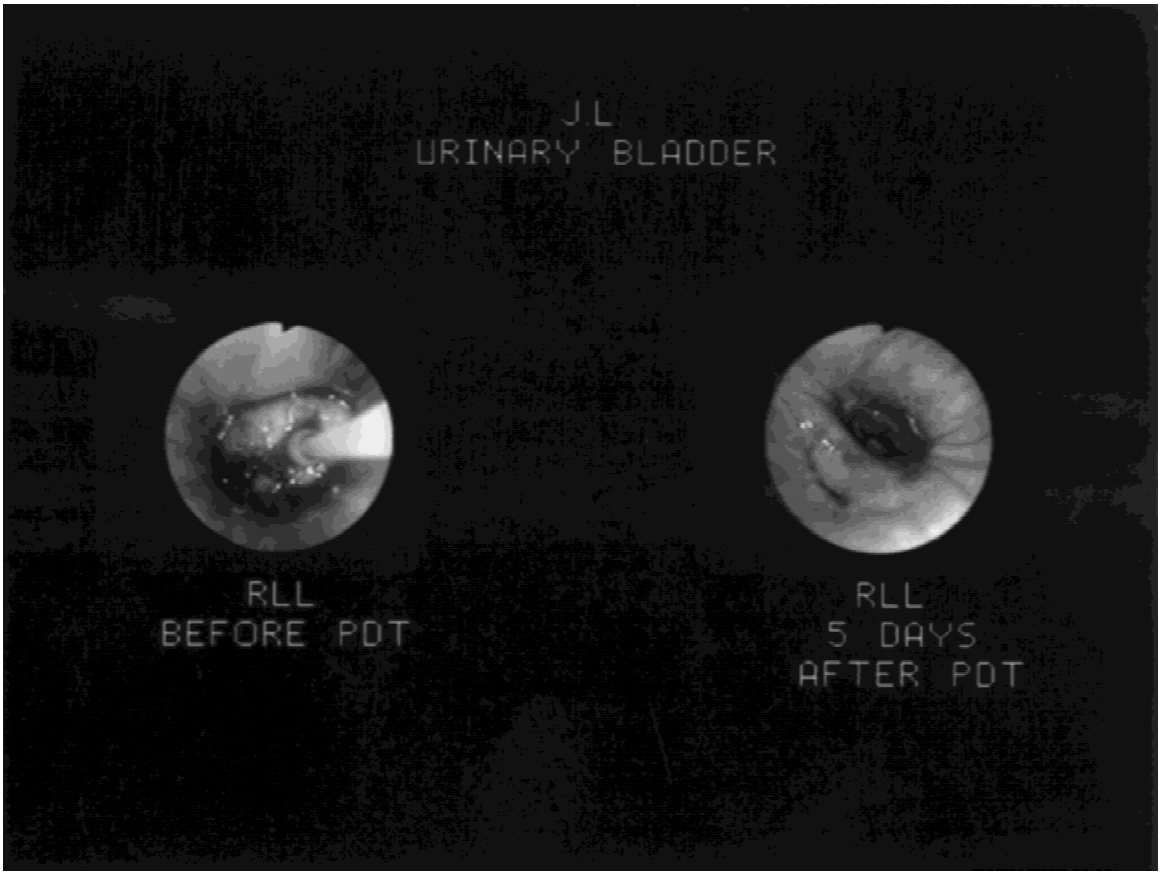

Fig. 1. The left shows a diffusing fiber inserted into a metastatic urinary bladder tumor in the right lower lobe bronchus to deliver photodynamic therapy. The right shows the same bronchus 5 days after PDT.

Berkeley, CA). Survival time in months was calculated from the time of the first PDT to the endpoint of death using Kaplan-Meier tables and curves. The Breslow-Gehan-Wilcoxon test compared the significance of differences of survival distributions between patients with metastatic endobronchial tumors and patients with stage IV primary endobronchial tumors.

Mann-Whitney U rank tests were used to compare the age and KPS of the two groups prior to PDT. Clinical effects of PDT on the 13 patients with metastatic endobronchial tumors were evaluated using Wilcoxon signed rank tests for the parameters of dyspnea, cough, hemoptysis, and KPS before and 1 month after PDT.

RESULTS

The estimated mean percent obstruction before the first PDT to 38 different endobronchial sites containing metastatic endobronchial tumors was 85% ± 25 SD and the mean percent obstruction at discharge after PDT was 13% ± 20 SD. The mean decrease was 72% and was statistically significant using the Wilcoxon signed rank test ($P < .0001$). Using the criteria of complete response (CR) = no remaining obstruction; partial response (PR) = 50 % reduction in obstruction, and some response (SR) = 20% reduction in obstruction, there was a 42% CR (16), 53% PR (20), and 5 % SR (2).

One month after PDT there was a statistically significant improvement in the level of dyspnea ($P = .012$), hemoptysis ($P = .028$), cough ($P = .027$), and KPS ($P = .020$) of patients with endobronchial metastases (Table 1).

The median survivals of patients with endobronchial metastases in months were: gallbladder (1) = 4; urinary bladder (1) = 8-still alive (Fig. 1); breast (3) = 17; colon (4) = 9 (Fig. 2); uterine leiomyosarcoma (3) = 24 (Fig. 3); renal (1) = 6 (Fig. 4).

The median age of metastatic endobronchial

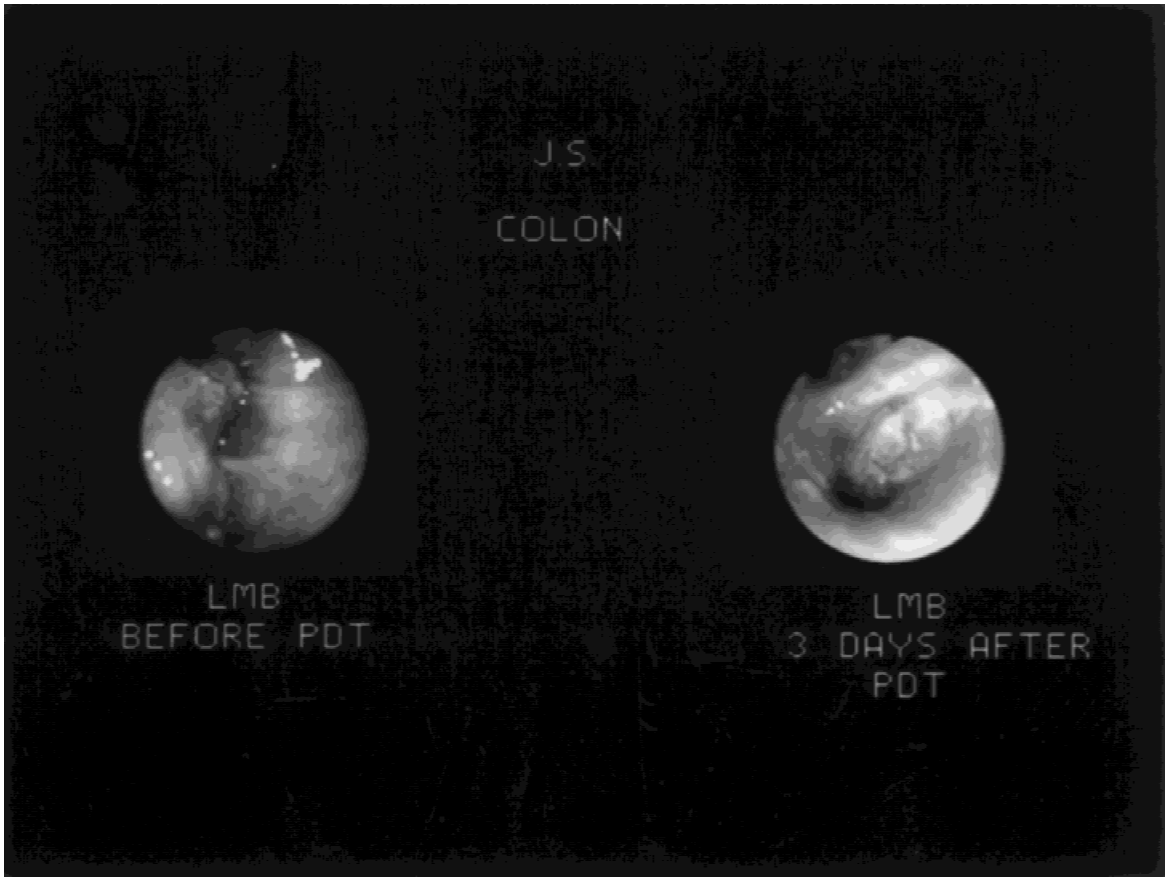

Fig. 2. The left shows a metastatic colon tumor obstructing the left main bronchus. The right shows the bronchus 3 days after PDT.

patients was 65 (mean = 67, range = 52–91) and of stage IV primary endobronchial patients was 64 (mean = 65, range = 51–83). The median pretreatment KPS of metastatic endobronchial patients was 60 (mean = 54, range = 20–80) and of stage IV primary endobronchial patients was 70 (mean = 60, range = 20–90). Thus the age (P = .965) and pretreatment KPS (P = .411) of stage IV primary endobronchial vs. metastatic endobronchial patients were not statistically different.

The mean time from diagnosis of the primary non-pulmonary tumor to PDT to the endobronchial metastases was 7 years (median = 7).

The cumulative survival after the first PDT of 13 patients with metastatic endobronchial tumors showed a median survival of 14 months which was significantly greater than the 4-month median survival of stage IV primary tumor patients treated with PDT (P = .008, Fig. 5).

DISCUSSION

The metastatic renal, colon, leiomyosarcoma, and gallbladder endobronchial tumors had a distinctly different appearance at endoscopy than primary squamous endobronchial tumors. They are more apt to be polypoid; pedunculated, globular, vascular, firm, well demarcated, and unattached except at their endobronchial origin. Once in the bronchus they take a path of least resistance and can protrude down several divisions. Thus a tumor obstructing a main bronchus may be arising from the apical segment of that lobe. Removing these back to their origin can provide immediate relief of obstructive and bleeding symptoms and increase the survival of patients succumbing to respiratory failure. The metastatic breast tumors were more similar in gross appearance to that of a primary squamous endobronchial tumor.

Udelsman et al. [3] reported on eight patients from the literature with soft tissue sarcomas metastatic to the endobronchus and added three of their own. Treatments varied but included radiation, chemotherapy, pulmonary resection, and radical pneumonectomy. The survival was reported for eight patients dead and one

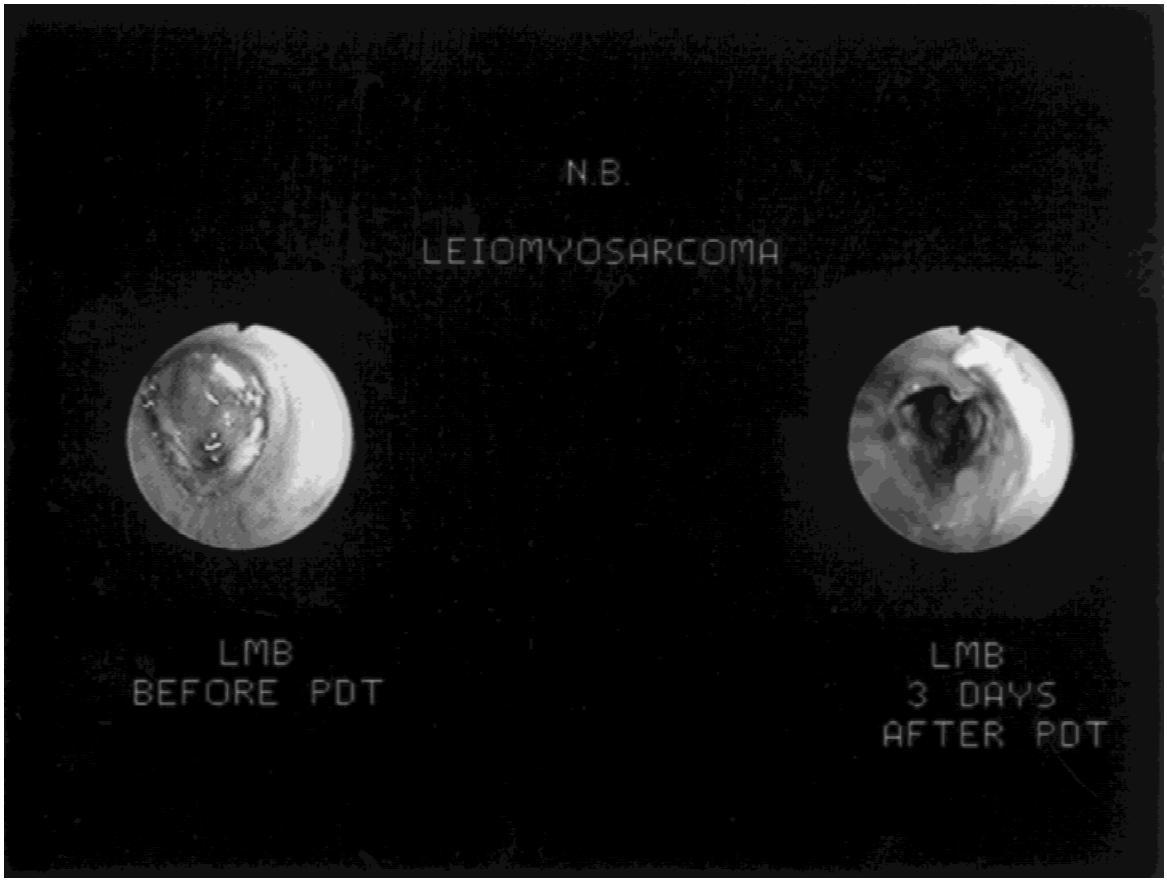

Fig. 3. The left shows a metastatic leiomyosarcoma tumor obstructing the left main bronchus. The right shows the bronchus 3 days after PDT.

alive at 11 months. The mean survival was 6 months (median = 3 months). Three patients with metastatic uterine leiomyosarcoma survived 4 days (X-ray treatment), 2 months (no treatment), and 22 months (pneumonectomy).

Warren et al. [4] reported on four patients operated on for metastatic endobronchial leiomyosarcoma. One survived 5.5 years when lost to follow up. Three died at 7, 22, and 24 months.

Gerst et al. [5] reported a 2-year survival after re-section of endobronchial metastasis in a patient 8 years after a hysterectomy for leiomyosarcoma.

Heitmiller et al. [6] reported on 23 patients treated for endobronchial metastases from nonpulmonary neoplasms (11 with chemotherapy, five with external beam radiation, and four with combined chemo–X-ray, three with none). The mean survivals in months were breast (12) = 10, renal (4) = 12, colon (3) = 9, urinary bladder (1) = 1, thyroid (1) = 1, ovary (1) = 11, nasopharyngeal (1) = 19.

Carlin et al. [7] reported nine cases of colorectal carcinoma metastatic to the tracheobronchial tree treated with Nd-Yag laser debulking. Four patients were alive with a mean survival of 15 months (median = 17) and five were dead with mean survival of 10 months (median = 8).

Kreisman et al. [8] reviewed the charts of 660 patients with breast cancer over a 5-year period; 119 had thoracic metastases and seven of these were endobronchial (1%).

Casino et al. [9] found an incidence of 2% endobronchial metastases in 2,388 bronchoscopies over an 8-year period.

Although considered rare by autopsy reports, it appears the incidence of metastatic endobronchial tumors may be higher than previously expected before the use of fiberoptic endoscopy and endobronchial laser management became more available.

One of the mechanisms of tumor destruction by PDT is the thrombosis of tumor vessels, which permits the safe mechanical removal of the tumor (McCaughan et al. [10], Henderson et al. [11], Star et al. [12]).

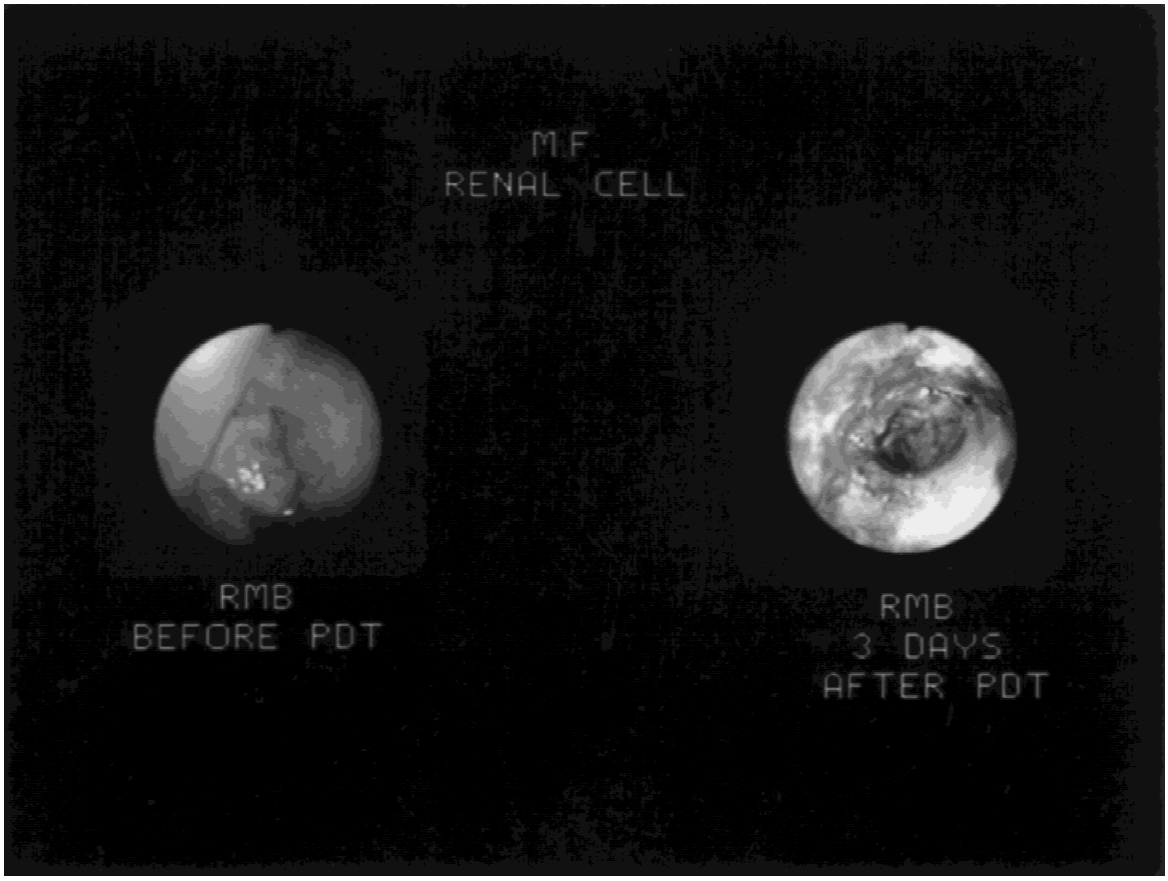

Fig. 4. The left shows a metastatic renal cell tumor obstructing the left main bronchus. The right shows the bronchus 3 days after PDT.

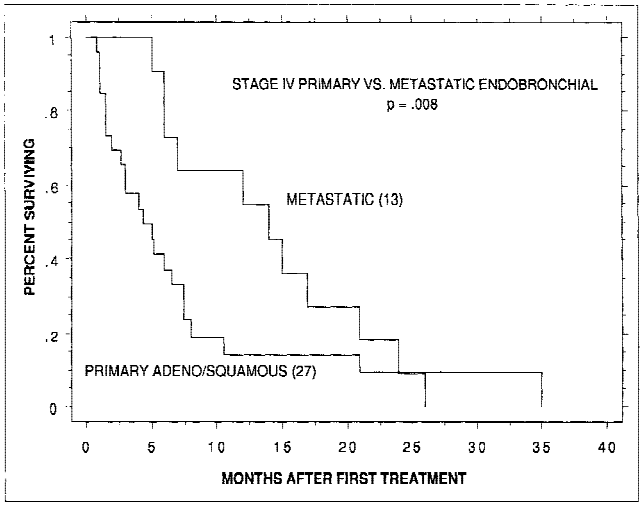

Fig. 5. Kaplan-Meier cumulative survival curves after PDT to endobronchial tumors. The Breslow-Gehan-Wilcoxon test ($P = .008$) showed a significant difference between primary stage IV and metastatic non-pulmonary endobronchial tumors. The number in parentheses equals the number of patients.

CONCLUSIONS

Cancer patients with pulmonary symptoms or obvious pulmonary metastases should be bronchoscoped. Chest X-rays will not demonstrate the endobronchial tumor. Significant improvement in the quality of life and survival time can be obtained by removing the endobronchial component of the tumors. These patients should not be denied therapy just because they have metastases elsewhere. They do very well because, in contrast to primary endobronchial cancer, the rest of their bronchial tree is usually not directly involved and they are symptomatic from obstruction and/or bleeding. Photodynamic therapy of endobronchial metastatic tumors provides a technique to improve the quality of life and prolong the survival of these patients.

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